EXPRESSION AND FUNCTION OF THE BRADYKININ B1 RECEPTOR IN NORMAL AND INFLAMED HUMAN GALLBLADDER

Eunice Andre[1], David Gazzieri[1], Elisabetta Bardella[1], Juliano Ferreira[3], Marcelo A. Mori[4], Michael Bader[4], João B.Calixto[5], Roberto De Giorgio[6], Roberto Corinaldesi[6], Pierangelo Geppetti[1] and Marcello Trevisani[1]

[1]Pharmacology Unit, University of Ferrara, [3]Dep. of Chemistry, Universidade Federal de Santa Maria, [4]Max Delbrück Center for Molecular Medicine, Berlin-Buch, [5]Dep. of Pharmacology, Universidade Federal de Santa Catarina, Florianópolis, [6] Dep. Int. Med. and Gastroent., University of Bologna

Background & Aims: We have recently described that bradykinin B_2 receptors are functionally expressed in the human gallbladder and that their activation induces a powerful contraction, increased in cholecystitis tissues. Here we investigated the presence and the role of B_1 receptors in the contractility of control and inflamed human gallbladder. ***Methods:*** Strips of control and acute cholecystitis human were processed for reverse-transcription polymerase chain reaction (RT-PCR) analysis or used *in vitro* in organ bath. ***Results:*** Lys-DBK concentration-dependently contracted strips of control and inflamed gallbladders (pD_2= 6.08±0.04 and pD_2= 6.06±0.05, respectively). The maximal effect of Lys-DBK-evoked contraction was higher in inflamed gallbladders (498.4±66.8 mg, n=8, vs. controls 313.2±34.3 mg, n=7, P<0.05). Lys-DBK-induced contraction was not altered by pretreatment with the selective bradykinin B_2 receptor antagonist, HOE140 (1 μM), the combination of NK_1 (SR140333), NK_2 (SR48968) and NK_3 (SR142801) tachykinin receptor antagonists (all 1 μM), the muscarinic acetylcholine receptor antagonist, atropine (1 μM) and the cyclooxygenase inhibitor, indomethacin (5 μM). In contrast, Lys-DBK-induced contraction was inhibited by the selective B_1 receptor antagonist, R-715 (1 μM). Quantitative RT-PCR analysis indicated that B_1 receptor mRNA levels was four-fold higher in cholecystitis specimens than in control tissues. To thoroughly confirm the cooperation of B_1 and B_2 receptors in the contractile function in human inflamed gallbladder, the inhibitory effect of R-715 (1 μM) or HOE140 (1 μM) was studied against the effect the B_2 agonist, Lys-BK (1 μM), that can be degraded to the B_1 agonist Lys-DBK. The independent application of R-715 (1 μM) or HOE140 (1 μM) partially prevented Lys-BK-induced contraction (25% and 35% of inhibition, respectively). However, combination of R-715 and HOE140 resulted in complete inhibition. ***Conclusions:*** The current results expand and strengthen previous data of the potential role of the kinin system in the regulation of contractility of the human gallbladder in health and disease. In particular, in cholecystitis human gallbladders not only the B_2 receptor is upregulated and mediates kinin evoked exaggerated contraction of the tissue, but also overexpression of the B_1 receptor could contribute to the spasmogenic effects of kinins abundantly produced by resident or blood-borne kininogens. Thus, selective antagonists of kinins receptors might have therapeutic efficacy to control spasms and inflammation in patients with acute cholecystitis.